Cell Stem Cell
Perspective

Target Populations for First-In-Human Embryonic Stem Cell Research in Spinal Cord Injury

Frédéric Bretzner,[1,*] Frédéric Gilbert,[4] Françoise Baylis,[2] and Robert M. Brownstone[1,3]
[1]Department of Anatomy and Neurobiology
[2]Departments of Philosophy and Obstetrics and Gynaecology
[3]Department of Surgery (Neurosurgery)
Dalhousie University, Halifax, Nova Scotia B3H 3J5, Canada
[4]Ethics and Bionics/Nanomedicine, ACES, University of Tasmania, Hobart 7005, Australia
*Correspondence: frederic.bretzner@dal.ca
DOI 10.1016/j.stem.2011.04.012

Geron recently announced that it had begun enrolling patients in the world's first-in-human clinical trial involving cells derived from human embryonic stem cells (hESCs). This trial raises important questions regarding the future of hESC-based therapies, especially in spinal cord injury (SCI) patients. We address some safety and efficacy concerns with this research, as well as the ethics of fair subject selection. We consider other populations that might be better for this research: chronic complete SCI patients for a safety trial, subacute incomplete SCI patients for an efficacy trial, and perhaps primary progressive multiple sclerosis (MS) patients for a combined safety and efficacy trial.

In January 2009, the U.S. Food and Drug Administration (FDA) approved Geron's first-in-human embryonic stem cell (hESC) clinical trial in patients with subacute American Spinal Injury Association (ASIA) Impairment Scale grade A thoracic spinal cord injury (SCI) (hereafter, complete SCI) (Geron, 2009a). Then, in August 2009, the FDA placed the trial on hold (before any patients had been enrolled) because of concerns about the risk of cyst formation at the injury site (Geron, 2009b). In July 2010 the clinical hold was lifted, and in October 2010 Geron announced that it had begun to enroll patients in its Phase 1 clinical trial (Geron, 2010a).

Typically, a Phase 1 clinical trial aims "to assess the safety and feasibility of the investigational intervention and to determine dosages for subsequent clinical trials. Direct therapeutic benefit, although hoped for, is unlikely in early trials, particularly if the first participants receive low doses" (Lo et al., 2005). Geron's Phase 1 clinical trial of hESC-derived oligodendrocyte progenitor cells (GRNOPC1) involves one injection of 2 million GRNOPC1 cells into patients within 7–14 days postinjury. The primary endpoint for the trial is safety ("as measured by the frequency and severity of adverse events within 1 year of GRNOPC1 injection that are related to GRNOPC1, the injection procedure used to administer GRNOPC1, and/or the concomitant immunosuppression administered"); however, Geron identifies efficacy as a secondary endpoint ("as measured by sensory scores and lower extremity motor scores on International Standards for Neurological Classification of Spinal Cord Injury [ISNCSCI] examinations") (Geron, 2010c). This secondary endpoint is noteworthy insofar as it likely explains the choice of subacute complete SCI patients as the target population.

Fair subject selection is a requirement for ethical clinical research (WMA, 2008; Emanuel et al., 2000; Levine, 1988). In this article we critically examine this aspect of trial design and suggest that while there are sound reasons to have chosen subacute complete SCI patients as the target population, there are both scientific and ethical reasons why a different patient population—chronic complete SCI patients, subacute incomplete SCI patients, or patients with primary progressive multiple sclerosis (MS) with spinal lesions—might have been a more appropriate target.

Patients with Subacute Complete SCI

Following injury, the spinal cord undergoes a cascade of changes within hours, days, months, and years. The resulting axonal disruption stops the bidirectional flow of information between the brain and spinal neuronal networks beyond the lesion site. In addition, animal models of SCI have shown that at the level of the lesion, spared axons undergo extensive but transient demyelination, and injured neurons undergo degenerative processes that can lead to cell death.

In the last two decades, the scientific community has shown in animal models that glial cell transplants can exhibit neuroprotective effects on the spinal cord after injury. These transplants may spare axons and neurons that could have been harmed by SCI by reducing the lesion size and the inflammatory reaction, by delivering trophic support, and/or by remyelinating axons in the vicinity of the injury (for review, see Tetzlaff et al., 2010). More recently, Keirstead and colleagues have demonstrated that hESC-derived GRNOPC1—a type of glial cell—remyelinates spared axons in addition to promoting functional recovery of forelimb-hindlimb coordination in a rat model of subacute *incomplete* thoracic SCI (Cloutier et al., 2006; Keirstead et al., 2005).

Despite some concerns from the scientific community regarding the absence of replication of the preclinical evidence in independent laboratories and in large animal models of SCI (e.g. cat, dog, rabbit, or primate) whose anatomy is closer to that of human (Courtine et al., 2007; Moon and Bunge, 2005; Kwon et al., 2010), Geron has moved forward to the first-in-human hESC clinical trial. In a recent survey, the majority of scientists called for independent replication as well as large animal models to demonstrate safety and efficacy of a cell transplant therapy prior to clinical translation (Kwon et al., 2010).

With the first hESC clinical trial, Geron aims to assess the safety of hESC-derived GRNOPC1 as well as the potential of

these cells to myelinate axons of the central nervous system and promote behavioral recovery in patients with subacute *complete* thoracic SCI. The clinical trial is designed to replicate part of the original study in rodents in targeting a SCI patient population at a similar level (thoracic) and within a similar time frame (1–2 weeks postinjury, which is referred to as a subacute period). According to Geron, ''Patients eligible for the Phase 1 trial must have documented evidence of functionally complete SCI with a neurological level of T3 to T10 spinal segments and agree to have GRNOPC1 injected into the lesion sites between seven and 14 days after injury'' (Geron, 2010a). However, one critical difference between the animal studies and the human trials is the injury type. In the animal studies, the cells were tested in rodents with *incomplete* SCI; in the clinical trials, the cells will be tested in humans with *complete* SCI.

Patients with complete SCI with a neurological level of T3 to T10 spinal segments exhibit a total lack of sensory, motor, and autonomic (including bladder and bowel) functions below their trunk and in their legs. In patients with incomplete SCI, some neurologic function remains. In the long term, patients with SCI are susceptible to developing medical complications such as pressure sores, chronic pain, and respiratory, cardiovascular, and bone problems. Successful recovery depends upon how well these chronic conditions are ameliorated.

An Appropriate Target Population?

A significant problem with the chosen target population, patients with subacute complete SCI, is that the transplanted hESC-derived GRNOPC1 (along with systemic immunosuppression) might impair spontaneous recovery in a subset of trial participants. Six to ten percent of patients initially assessed as complete SCI show spontaneous functional improvement over time, suggesting the initial lesion was incomplete (Burns et al., 2003; Consortium for Spinal Cord Medicine, 2000; Maynard et al., 1979). Spontaneous recovery in this population (i.e., patients with incomplete SCI initially diagnosed as complete SCI) might be jeopardized by participation in the GRNOPC1 trial. These patients would undergo a second surgery to transplant the cells within 1–2 weeks after the initial SCI, following a first operation to decompress the spinal cord and/or stabilize the spine. In addition to the research risks of cell transplantation and immunosuppression, this second surgery would expose patients to additional neurosurgical risks, including extending the lesion while transplanting the cells or introducing infection. In this way, trial participation would disadvantage (some) patients relative to the standard of competent care otherwise available to them outside the trial (Anderson and Kimmelman, 2010).

Further, it is important to understand that patients with subacute complete SCI are a vulnerable population. Seven to 14 days postinjury, which is the recruitment period for the Geron trial, is a time during which the patients who will have suffered an acute traumatic event will be experiencing stress, anxiety, fear, and depression in degrees proportionate to the severity of injury (Dryden et al., 2005; Illes et al., 2011; Kennedy and Rogers, 2000). These patients will have had little time to reflect on their changed life circumstances and to fully understand and appreciate the risks of participating in a first-in-human hESC clinical trial. Moreover, these patients may be desperate for any opportunity to reverse their misfortune and as such may be eager to agree to participate in research without fully understanding and appreciating the consequences of their decision.

The Declaration of Helsinki states:

> Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence (WMA, 2008).

This is not a directive to exclude vulnerable populations from research, but rather a call to pay particular attention to the risk of coercion or undue influence. With this risk there is the worry that one of the elements of free and informed choice, namely voluntariness, will be compromised. In addition to the risk of coercion or undue influence, there is also the risk of exploitation (Ruof, 2004). With this risk, the concern is with the degree to which people might be used to serve the interests of others.

With the Geron hESC-derived GRNOPC1 trial, we do not imagine that patients with subacute complete SCI will be coerced into research participation. We do imagine, however, that recently diagnosed complete SCI patients—as compared with chronic complete SCI patients or patients with primary progressive MS with spinal lesions—may be more vulnerable to undue influence and possibly exploitation (where exploitation involves taking unfair advantage of another). For example, as Miller and Rosenstein remark, ''Insofar as patient-subjects confuse research with therapy, they do not accurately comprehend what they are doing and thus may be vulnerable to exploitation'' (Miller and Rosenstein, 2003).

Subacute complete SCI patients are at increased risk of conflating participating in a clinical trial with accessing novel medical treatment(s), a phenomenon known as the therapeutic misconception (Gilbert, 2009; Miller and Rosenstein, 2003). To be more precise, these patients, who suddenly and unexpectedly find themselves in dire circumstances, may fail to appreciate the disadvantages associated with trial participation, where protocol design (not the needs or interests of patients) determines what interventions patients (once they are trial participants) will receive (Appelbaum et al., 1987; Kimmelman, 2007).

In general, first-in-human clinical trials aim to produce socially valuable medical knowledge; they do not serve therapeutic functions (Anderson and Kimmelman, 2010). And in particular, Geron's first-in-human Phase 1 hESC-derived GRNOPC1 clinical trial is about contributing to generalizable knowledge, not about delivering cutting-edge stem cell therapy. It is doubtful, however, that subacute complete SCI patients would understand the invitation to enroll in Geron's trial in these terms, unless the consent process unambiguously explained that clinical benefits were highly unlikely, and that ''the value of the knowledge sought, rather than the product's therapeutic activity'' (Kimmelman and London, 2011) justified the move from preclinical to clinical research.

Indeed, the risk of therapeutic misconception (i.e., conflating care and research) is likely to be high among patients recently diagnosed with complete SCI who, in the immediate

posttraumatic period, likely will expect nothing less of their clinicians than medical advice aimed at promoting their recovery (as contrasted with advice aimed at producing medical knowledge to benefit society). It is our contention that, in general, patients with subacute complete SCI are unlikely to fully understand and appreciate that trial participation means the needs and interests of science, not their personal needs and interests, will determine the "care" they receive.

In addition to the therapeutic misconception, there is the misestimation of harms and benefits. To be clear, even if subacute complete SCI patients understand (and appreciate) the difference between research and therapy, in the immediate postinjury period they very likely will underestimate the potential harms and overestimate the potential benefits of research participation, resulting in a mistaken understanding of the harm-benefit ratio. As Christopher Thomas Scott astutely noted,

> Newly disabled persons (and the surrogates and families who care for them) may overestimate the long-term emotional impact of a recent injury. As a result, participants might be more likely to agree to a trial now than they would after time passes and their expectations change. For those living with a debilitating or deadly disease, a person's hope for an incremental benefit from a safety trial—however remote—might outweigh any considerations of risk. Restoration of bowel function for a patient with a spinal injury represents a significant improvement in quality of life. On the other hand, an inoperable tumor caused by the transplant may mean a lifetime of peripheral pain (Scott, 2008).

Here, it is important to stress that the potential harms associated with the Geron trial are not insignificant. In addition to the surgical risks of extending the lesion while transplanting the cells and of infection, there are the risks of (1) preventing endogenous remyelination, (2) promoting teratoma formation, (3) affecting inflammation, and (4) promoting aberrant neural reorganization.

First, hESC-derived GRNOPC1 transplantation could be hazardous in humans because GRNOPC1 transplants may be in direct competition with endogenous progenitor-derived glial cells. The expected benefit of GRNOPC1 resides in their potential to remyelinate axons after SCI (Cloutier et al., 2006; Keirstead et al., 2005). Although the injured spinal cord undergoes demyelination of spared axons shortly following SCI, recent studies of mouse and primate SCI have reported that axons are eventually remyelinated by cells derived from endogenous progenitors (Lasiene et al., 2008; Meletis et al., 2008; Sellers et al., 2009; Yang et al., 2006). This suggests there is no chronic demyelination after SCI. In humans, the role of persistent demyelination in neurologic dysfunction following SCI is not clear: no progressive chronic demyelination has been reported to date, and persistent demyelination was reported in only a fraction of patients (Guest et al., 2005; Kakulas, 1999; Norenberg et al., 2004).

Second, there is a risk of teratoma formation generated by undifferentiated hESCs. While differentiated stem cells (GRNOPC1) do not seem to degenerate or migrate away from the injection site in the rat (Cloutier et al., 2006; Coutts and Keirstead, 2008; Keirstead et al., 2005), undifferentiated stem cells can be harmful in nonhuman animals (Hofstetter et al., 2005) as well as in humans (Amariglio et al., 2009; Dobkin et al., 2006). Some incidences of tumors have been reported after transplantations of predifferentiated hESCs in the brain (Brederlau et al., 2006; Erdö et al., 2003; Roy et al., 2006). These undifferentiated hESCs could originate from cells incompletely differentiated before transplantation as well as from transplanted cells that could dedifferentiate in the injured spinal cord. A few undifferentiated stem cells might be sufficient to generate tumors at the lesion site or at distant healthy regions of the central nervous system. The cells could also be quiescent for months or years before developing teratomata or teratocarcinomas (Knoepfler, 2009). However, it is reassuring to note that Geron extensively investigated the number of residual undifferentiated stem cells required for teratoma formation in an immunocompromised rodent (dose response) and that no teratomata were reported by Geron 12 months after GRNOPC1 transplants in the animal model (Geron, 2010b).

Third, GRNOPC1 transplants could affect the inflammation that occurs following SCI. In animal models of SCI (Hausmann, 2003; Popovich et al., 1997; Schnell et al., 1999; Sroga et al., 2003), neutrophils, macrophages, and microglia are believed to contribute sequentially to inflammation that could cause tissue damage by releasing oxidative and proteolytic enzymes (Taoka et al., 1997), as well as proinflammatory cytokines, reactive oxygen species, nitric oxide, and proteases (Popovich et al., 1999, 2002). Similar inflammation has also been reported in subacute and chronic spinal cord injuries in humans (Chang, 2007; Fleming et al., 2006; Yang et al., 2004). However, despite extensive studies in the last 15 years, the role of inflammation in SCI is still not understood. Indeed, both anti-inflammatory and proinflammatory treatments have been reported to improve recovery from SCI (for review, see Gensel et al., 2011; Schwartz and Yoles, 2006). There are several examples in animal models of SCI in which transplantation of adult progenitor cells (Busch et al., 2011; Kovacsovics-Bankowski et al., 2009) or ESCs in conjunction with immunosuppression (Bottai et al., 2010; Hill et al., 2004) into the spinal cord has led to a reduction in inflammation and demyelination and, in turn, the promotion of axonal regeneration. If GRNOPC1 transplants likewise reduce inflammation after SCI, this may in fact affect recovery of function through aberrant sprouting (see below). Furthermore, it is possible that the inflammatory processes themselves could change the fate of transplanted GRNOPC1 cells by differentiating and/or dedifferentiating them. It is therefore important to determine the relationship between hESC-derived GRNOPC1 cells and inflammation and whether any modulation of these processes is functionally beneficial or detrimental.

Fourth, the presence of either undifferentiated hESCs and/or inappropriate inflammation may trigger aberrant changes to central nervous system networks that could lead to neurologic dysfunction, such as hyperreflexia, spasticity, dystonia, pain, or allodynia (Dobkin et al., 2006; Hofstetter et al., 2005). For instance, transplantation of adult neural stem cells into a rat thoracic SCI model has been reported to improve motor recovery, but also to cause aberrant axonal sprouting associated with allodynia-like hypersensitivity of forepaws. Although no allodynia (pain induced by normally nonnoxious stimuli) has been reported in response to cold and mechanical stimuli in the animal

model of GRNOPC1 transplants (Geron, 2010b), it is not known whether abnormal neural reorganization leading to other symptoms and signs would occur.

To be sure, Geron has sought to minimize these potential harms—harms that would apply with any first-in-human trial of hESC-derived GRNOPC1, regardless of the target population. For example, Geron screened for undifferentiated hESCs, teratoma formation, and potential allodynia in response to cold and mechanical stimuli (Geron, 2010b). What is less clear is what efforts have been made by Geron to minimize the risk that prospective trial participants will overestimate the potential benefits of this first-in-human trial, especially in a context where there has been overwhelmingly positive media coverage and endorsement from patient groups suggesting that stem cell cures are just around the corner (Chien, 2004; Nature, 2004a; Nature Neuroscience, 2004b; Hall, 2008; Illes et al., 2011; Lau et al., 2008; Wade, 2005). The average person's ability to distinguish hype from hope is limited at the best of times and is not likely to be particularly effective when faced with the prospect of paralysis. This is hardly a circumstance that invites a skeptical review of enthusiastic news reporting. Add to this the fact that Geron's Phase 1 trial includes secondary endpoints that typically would be part of a Phase 2 trial, namely "improved neuromuscular control or sensation in the trunk or lower extremities" (Geron, 2010a), and patients could be forgiven for thinking that there was a clear favorable harm-benefit ratio, which is not the case.

An Alternative for Studying Safety: Chronic Complete SCI Patients

The usual primary goal of a Phase 1 clinical trial is to assess safety. Chronic complete SCI patients may be a more preferable target population than subacute complete SCI patients in which to assess the *safety* of hESC-derived GRNOPC1.

Confirmation that the lesion is complete prior to research participation would ensure a stable environment in which to assess the safety of hESC-derived GRNOPC1. The processes underlying secondary injury of the spinal cord terminate after several months (Alexander and Popovich, 2009; Steeves et al., 2007), leading to a stable environment that may be less likely to trigger adverse reactions. In addition, patients with chronic injury will have had time to adjust to their life with paraplegia, which could help diminish the risk of therapeutic misconception and moderate the misestimation of harms and benefits. Usually, an injury is considered chronic when patients have reached a plateau and an improvement in function is unlikely. Typically, this is several months after injury.

Together, these facts—stable environment in which to assess safety, diminished risk of therapeutic misconception, and moderated risk of misestimation of harms and benefits—suggest that there may be fewer ethical qualms in proceeding with research involving chronic complete SCI patients than with research involving subacute complete SCI patients because of a more favorable harm-benefit ratio. The reduced risk of therapeutic misconception and therapeutic misestimation equates with reduced potential harm to patients, and the better environment in which to assess safety equates with increased potential benefit to society and the SCI community. Beyond this, if there were therapeutic benefits for chronic complete SCI patients from trial participation (notwithstanding preclinical findings to the contrary), these would be clearer and more readily quantifiable, as there would be a stable baseline neurologic status preceding transplantation. This approach would appear to be in line with a recently announced clinical trial by Stem Cells, Inc., in which 12 patients with chronic SCI will receive implantation of human fetal neural cells. The study will progress from complete to incomplete SCI populations (Globe Newswire, 2011).

An argument against conducting a "strict" safety trial of GRNOPC1 in a chronic complete SCI population is that patients with subacute complete SCI would be denied the benefits of research participation. This argument is flawed, however, insofar as it wrongly presumes that the cells will be proven safe and that a first-in-human clinical trial in chronic complete SCI patients would only serve to deny subacute complete SCI patients access to a potentially effective stem cell intervention. Fair subject selection is not about ensuring that everyone has the same opportunity to expose themselves to the potential harms of research. Rather, it is about selecting for trial participation the least vulnerable population that can usefully answer the research question. It is our contention that with respect to questions about the safety and feasibility of GRNOPC1 transplantation, chronic complete SCI patients are less vulnerable than subacute complete SCI patients. Further, by proceeding in a stepwise manner as the data warrant (from the less vulnerable patient population to the more vulnerable patient population), the field of stem cell research may experience fewer setbacks in the long term in the event of unexpected, untoward outcomes (cf. gene transfer trials [Kimmelman et al., 2006]), in which case going more slowly at the outset could ultimately lead more quickly to therapies proven safe and effective.

An Alternative for Studying Efficacy: Subacute Incomplete SCI Patients

While efficacy is usually the primary goal of a Phase 2 clinical trial, the Phase 1 Geron trial of hESC-derived GRNOPC1 includes efficacy as a secondary endpoint (Geron, 2010c). Subacute incomplete SCI patients may be a more preferable target population than chronic complete and subacute complete SCI patients in which to assess the *efficacy* of hESC-derived GRNOPC1.

It probably will be difficult to assess the efficacy of hESC-derived GRNOPC1 with chronic complete SCI patients, as the chronicity and completeness of the lesion might reduce the statistical power of an efficacy trial. Given that 10% percent of the complete SCI population exhibit some spontaneous functional improvement (Burns et al., 2003; Consortium for Spinal Cord Medicine, 2000; Corbetta et al., 2002; Maynard et al., 1979), it might be expected that these are the patients with some axons intact, and hence they may be the ones to benefit from an early hESC-derived GRNOPC1 transplantation. However, because of this low proportion of people expected to show some benefit, a very large number of subacute complete SCI patients (i.e., the patient population in the Geron study) will be necessary to determine the degree of recovery that is spontaneous versus GRNOPC1 mediated. On the other hand, if effective, hESC-derived GRNOPC1 transplantation likely will promote functional recovery only in subacute incomplete SCI patients (Cloutier et al., 2006; Keirstead et al., 2005), presumably

by remyelinating spared axons along the injured spinal cord. If very rigid selection criteria are used to create a uniform patient pool from which functional outcomes can be interpreted, then the number of subacute incomplete SCI patients would be significantly smaller than that necessary if using a subacute complete SCI population. The subacute complete and subacute incomplete SCI patient populations likely are equally vulnerable in terms of the risk of undue influence and therapeutic misconception. However, as fewer patients would be needed to reach statistical significance in a trial involving subacute incomplete SCI patients, ethics behooves us to select this patient population, thereby minimizing the risk of harm over the population of trial participants.

An Alternative for Studying Safety and Efficacy: Patients with Primary Progressive MS with Spinal Lesions

We have recommended above two disparate patient populations for study: a chronic complete SCI population for a Phase 1 safety trial and a subacute incomplete SCI population for a Phase 2 efficacy trial (presumably following on a prior Phase 1 trial). Geron, having an interest in studying both safety and efficacy, has decided to proceed with a study involving a subacute complete SCI population, thereby apparently allowing the secondary goal of assessing efficacy to influence the choice of target population for its first-in-human trial of hESC-derived GRNOPC1. This brings us to the question: Is there a more suitable patient population for a combined safety and efficacy trial, if such a trial were approved by the FDA?

Geron has recently identified MS patients as a possible target population for hESC-derived GRNOPC1 transplants, and research in a nonhuman primate model of MS is currently underway (Geron, 2010a). In the context of our discussion about subject selection for the first-in-human trial of hESC-derived GRNOPC1, it behooves us to ask the question of whether MS patients might be a better target population for a combined safety and efficacy study than subacute complete SCI patients.

Since GRNOPC1 remyelinate dysmyelinated and demyelinated axons in several MS mouse models (Hardison et al., 2006; Nistor et al., 2005; Totoiu et al., 2004), it is tempting to speculate that MS patients might be a suitable population to assess the efficacy of GRNOPC1. One treatment aimed at improving conduction in demyelinated axons, 4-aminopyridine (Fampridine, Acorda Therapeutics or HP184, Aventis), showed no statistical improvements in SCI populations (Cardenas et al., 2007; DeForge et al., 2004; van der Bruggen et al., 2001), but led to positive functional outcomes in MS patients (Goodman et al., 2007, 2009). As such, MS patients appear to be more responsive than SCI patients to a pharmacologic treatment targeted to demyelinated axons.

The issue with cellular therapies for MS is that the demyelination in MS is not focal, but rather affects many regions of the central nervous system. MS can produce a wide range of symptoms affecting sensory, motor, autonomic, and cognitive functions. There are four main types of MS, with about 10%–15% of patients having primary progressive MS. This type usually develops initially in the spinal cord, and although it may occur in the brain, this is usually in the absence of disabling cognitive function. Primary progressive MS is characterized by a steady progression of the disease without relapses and remissions.

In primary progressive MS, there is relative stability (i.e., chronicity) of the symptoms, and neurological signs can be functionally ascribed to defined, presumably stable, spinal lesions. We therefore ask whether patients with primary progressive MS may be an appropriate target population for GRNOPC1 transplantation. Because of the chronicity of their disease, these patients may be less vulnerable to undue influence or exploitation owing to the risks of therapeutic misconception and misestimation of potential harms and benefits. That is, the above arguments supporting the enrollment of a chronic complete SCI population for a safety trial could be extended to this primary progressive MS population. In addition, with symptoms and signs directly attributable to defined spinal lesions, the arguments for targeting subacute incomplete SCI patients to study efficacy would hold. However, it must be stressed that prior to any clinical translation, research is needed to determine the safety and efficacy of GRNOPC1 transplants in an animal model of spinal MS such as the experimental autoimmune encephalomyelitis (EAE) model. If supporting data in such an animal model are obtained, it may be reasonable to offer this population participation in a clinical transplantation trial—had Geron so decided, one of those trials might have been for hESC-derived GRNOPC1.

Presumably this idea has occurred to Geron, since, as noted above, it is currently doing preclinical research in a nonhuman primate model of MS (Geron, 2010a). This raises an interesting ethical question: If, in general terms, a primary progressive MS patient population is less vulnerable to the risks of therapeutic misconception and misestimation of harms and benefits than a subacute complete SCI patient population, should Geron have delayed its first-in-human clinical trials to gather additional preclinical data in order to proceed with clinical research in a less vulnerable population? This is an important question to ask and answer, given the overriding ethical obligation to minimize the risk of harm for trial participants.

Conclusion

In summary, the choice of a suitable population for a first-in-human clinical trial of cell transplantation for SCI is very difficult. Geron's Phase 1 clinical trial of hESC-derived GRNOPC1, which aims to assess both safety and efficacy in a subacute complete SCI patient population, raises important scientific and ethical questions about the choice of target population. Focusing on safety (the usual primary endpoint of a Phase 1 trial), in conjunction with the goal of reducing avoidable risks of harm (and thereby enhancing the harm-benefit ratio), we think that chronic complete SCI patients would be a more suitable target population for hESC-derived GRNOPC1 transplants than subacute complete SCI patients. These patients are "less likely to suffer opportunity costs from study participation" (Kimmelman and London, 2011), which is an important ethical consideration when "knowledge value," not "therapeutic benefit," motivates the research. Focusing on efficacy (the usual primary endpoint for a Phase 2 trial), in conjunction with the goal of minimizing harm and maximizing benefit, subacute incomplete SCI patients would be a better target population than subacute complete SCI patients. These patients are more likely to exhibit functional improvements and thereby potentially benefit from trial participation. Finally, if both safety and efficacy are to be studied, then an equally good (or better) target population compared to

subacute complete SCI patients may be patients with primary progressive MS with symptoms and signs directly attributable to specific spinal cord lesions. Primary progressive MS patients with spinal lesions, who are refractory to current treatments, could potentially benefit from hESC-derived GRNOPC1 transplants through remyelinating their dysmyelinated spinal axons and thus gaining neurologic functions.

As Emanuel and colleagues note, "fair subject selection requires that the scientific goals of the study … be the primary basis for determining the groups and individuals that will be recruited and enrolled" (Emanuel et al., 2000). Persons are not to be enrolled in clinical trials because they are "compromised in their ability to protect themselves," especially when "people from less vulnerable groups could have met the scientific requirements of the study" (Emanuel et al., 2000). Our contention is that there are potentially less vulnerable target populations than persons with subacute complete SCI that could have been targeted for this research, allowing for one or both of the stated research objectives to be realized.

ACKNOWLEDGMENTS

We thank members of the NovelTechEthics research team at Dalhousie University, Renee Hartlieb, and anonymous reviewers for helpful comments on an earlier version of this paper. We also thank Philippe Magown for discussion and comments on the design of clinical trials and Virender Bhan for discussion about MS patients. This work was funded in part by the Canadian Institutes of Health Research (CIHR) NNF 80045, States of Mind: Emerging Issues in Neuroethics awarded to Françoise Baylis, Canada Research Chair in Bioethics and Philosophy. The spinal cord research of Robert Brownstone is supported by grants from the CIHR. At the time of writing, Frédéric Gilbert was a research postdoctoral fellow on the States of Mind grant. Frédéric Bretzner is a CIHR and Paralysis Project of America (PPA) postdoctoral fellow researcher.

REFERENCES

Alexander, J.K., and Popovich, P.G. (2009). Neuroinflammation in spinal cord injury: therapeutic targets for neuroprotection and regeneration. Prog. Brain Res. *175*, 125–137.

Amariglio, N., Hirshberg, A., Scheithauer, B.W., Cohen, Y., Loewenthal, R., Trakhtenbrot, L., Paz, N., Koren-Michowitz, M., Waldman, D., Leider-Trejo, L., et al. (2009). Donor-derived brain tumor following neural stem cell transplantation in an ataxia telangiectasia patient. PLoS Med. *6*, e1000029.

Anderson, J.A., and Kimmelman, J. (2010). Extending clinical equipoise to phase 1 trials involving patients: unresolved problems. Kennedy Inst. Ethics J. *20*, 75–98.

Appelbaum, P.S., Roth, L.H., Lidz, C.W., Benson, P., and Winslade, W. (1987). False hopes and best data: consent to research and the therapeutic misconception. Hastings Cent. Rep. *17*, 20–24.

Bottai, D., Cigognini, D., Madaschi, L., Adami, R., Nicora, E., Menarini, M., Di Giulio, A.M., and Gorio, A. (2010). Embryonic stem cells promote motor recovery and affect inflammatory cell infiltration in spinal cord injured mice. Exp. Neurol. *223*, 452–463.

Brederlau, A., Correia, A.S., Anisimov, S.V., Elmi, M., Paul, G., Roybon, L., Morizane, A., Bergquist, F., Riebe, I., Nannmark, U., et al. (2006). Transplantation of human embryonic stem cell-derived cells to a rat model of Parkinson's disease: effect of in vitro differentiation on graft survival and teratoma formation. Stem Cells *24*, 1433–1440.

Burns, A.S., Lee, B.S., Ditunno, J.F., Jr., and Tessler, A. (2003). Patient selection for clinical trials: the reliability of the early spinal cord injury examination. J. Neurotrauma *20*, 477–482.

Busch, S.A., Hamilton, J.A., Horn, K.P., Cuascut, F.X., Cutrone, R., Lehman, N., Deans, R.J., Ting, A.E., Mays, R.W., and Silver, J. (2011). Multipotent adult progenitor cells prevent macrophage-mediated axonal dieback and promote regrowth after spinal cord injury. J. Neurosci. *31*, 944–953.

Cardenas, D.D., Ditunno, J., Graziani, V., Jackson, A.B., Lammertse, D., Potter, P., Sipski, M., Cohen, R., and Blight, A.R. (2007). Phase 2 trial of sustained-release fampridine in chronic spinal cord injury. Spinal Cord *45*, 158–168.

Chang, H.T. (2007). Subacute human spinal cord contusion: few lymphocytes and many macrophages. Spinal Cord *45*, 174–182.

Chien, K.R. (2004). Stem cells: lost in translation. Nature *428*, 607–608.

Cloutier, F., Siegenthaler, M.M., Nistor, G., and Keirstead, H.S. (2006). Transplantation of human embryonic stem cell-derived oligodendrocyte progenitors into rat spinal cord injuries does not cause harm. Regen. Med. *1*, 469–479.

Consortium for Spinal Cord Medicine. (2000). Outcomes following traumatic spinal cord injury: clinical practice guidelines for health-care professionals. J. Spinal Cord Med. *23*, 289–316.

Corbetta, M., Burton, H., Sinclair, R.J., Conturo, T.E., Akbudak, E., and McDonald, J.W. (2002). Functional reorganization and stability of somatosensory-motor cortical topography in a tetraplegic subject with late recovery. Proc. Natl. Acad. Sci. USA *99*, 17066–17071.

Courtine, G., Bunge, M.B., Fawcett, J.W., Grossman, R.G., Kaas, J.H., Lemon, R., Maier, I., Martin, J., Nudo, R.J., Ramon-Cueto, A., et al. (2007). Can experiments in nonhuman primates expedite the translation of treatments for spinal cord injury in humans? Nat. Med. *13*, 561–566.

Coutts, M., and Keirstead, H.S. (2008). Stem cells for the treatment of spinal cord injury. Exp. Neurol. *209*, 368–377.

DeForge, D., Nymark, J., Lemaire, E., Gardner, S., Hunt, M., Martel, L., Curran, D., and Barbeau, H. (2004). Effect of 4-aminopyridine on gait in ambulatory spinal cord injuries: a double-blind, placebo-controlled, crossover trial. Spinal Cord *42*, 674–685.

Dobkin, B.H., Curt, A., and Guest, J. (2006). Cellular transplants in China: observational study from the largest human experiment in chronic spinal cord injury. Neurorehabil. Neural Repair *20*, 5–13.

Dryden, D.M., Saunders, L.D., Rowe, B.H., May, L.A., Yiannakoulias, N., Svenson, L.W., Schopflocher, D.P., and Voaklander, D.C. (2005). Depression following traumatic spinal cord injury. Neuroepidemiology *25*, 55–61.

Emanuel, E.J., Wendler, D., and Grady, C. (2000). What makes clinical research ethical? JAMA *283*, 2701–2711.

Erdö, F., Bührle, C., Blunk, J., Hoehn, M., Xia, Y., Fleischmann, B., Föcking, M., Küstermann, E., Kolossov, E., Hescheler, J., et al. (2003). Host-dependent tumorigenesis of embryonic stem cell transplantation in experimental stroke. J. Cereb. Blood Flow Metab. *23*, 780–785.

Fleming, J.C., Norenberg, M.D., Ramsay, D.A., Dekaban, G.A., Marcillo, A.E., Saenz, A.D., Pasquale-Styles, M., Dietrich, W.D., and Weaver, L.C. (2006). The cellular inflammatory response in human spinal cords after injury. Brain *129*, 3249–3269.

Gensel, J.C., Donnelly, D.J., and Popovich, P.G. (2011). Spinal cord injury therapies in humans: an overview of current clinical trials and their potential effects on intrinsic CNS macrophages. Expert Opin. Ther. Targets *15*, 505–518.

Geron (2009a). Geron receives FDA clearance to begin world's first human clinical trial of embryonic stem cell-based therapy (http://www.geron.com/media/pressview.aspx?id=1148).

Geron (2009b). Geron comments on FDA hold on spinal cord injury trial (http://www.geron.com/media/pressview.aspx?id=1188).

Geron (2010a). Geron to proceed with first human clinical trial of embryonic stem cell-based therapy (http://www.geron.com/media/pressview.aspx?id=1229).

Geron (2010b). Preclinical Safety studies (http://www.geron.com/GRNOPC1Trial/grnopc1-sec3.html).

Geron (2010c). Phase 1 Safety Study of GRNOPC1 in Patients with Neurologically Complete, Subacute, Spinal Cord Injury (http://clinicaltrials.gov/archive/NCT01217008/2010_10_07).

Gilbert, F. (2009). Geron's hESC trial for spinal cord injury: the risk of therapeutic misconception. Bioethics Forum (http://www.thehastingscenter.org/Bioethicsforum/Post.aspx?id=3370).

Globe Newswire (2011). Stem Cells, Inc. initiates world's first neural stem cell trial in spinal cord injury. MSNBC. Retrieved March 18, 2011 from http://www.msnbc.msn.com/id/42069437.

Goodman, A.D., Cohen, J.A., Cross, A., Vollmer, T., Rizzo, M., Cohen, R., Marinucci, L., and Blight, A.R. (2007). Fampridine-SR in multiple sclerosis: a randomized, double-blind, placebo-controlled, dose-ranging study. Mult. Scler. *13*, 357–368.

Goodman, A.D., Brown, T.R., Krupp, L.B., Schapiro, R.T., Schwid, S.R., Cohen, R., Marinucci, L.N., and Blight, A.R.; Fampridine MS-F203 Investigators. (2009). Sustained-release oral fampridine in multiple sclerosis: a randomised, double-blind, controlled trial. Lancet *373*, 732–738.

Guest, J.D., Hiester, E.D., and Bunge, R.P. (2005). Demyelination and Schwann cell responses adjacent to injury epicenter cavities following chronic human spinal cord injury. Exp. Neurol. *192*, 384–393.

Hall, V.J. (2008). Embryonic stem cells and Parkinson's disease: cell transplantation to cell therapy. Ann. Acad. Med. Singapore *37*, 162–163.

Hardison, J.L., Nistor, G., Gonzalez, R., Keirstead, H.S., and Lane, T.E. (2006). Transplantation of glial-committed progenitor cells into a viral model of multiple sclerosis induces remyelination in the absence of an attenuated inflammatory response. Exp. Neurol. *197*, 420–429.

Hausmann, O.N. (2003). Post-traumatic inflammation following spinal cord injury. Spinal Cord *41*, 369–378.

Hill, C.E., Proschel, C., Noble, M., Mayer-Proschel, M., Gensel, J.C., Beattie, M.S., and Bresnahan, J.C. (2004). Acute transplantation of glial-restricted precursor cells into spinal cord contusion injuries: survival, differentiation, and effects on lesion environment and axonal regeneration. Exp. Neurol. *190*, 289–310.

Hofstetter, C.P., Holmström, N.A., Lilja, J.A., Schweinhardt, P., Hao, J., Spenger, C., Wiesenfeld-Hallin, Z., Kurpad, S.N., Frisén, J., and Olson, L. (2005). Allodynia limits the usefulness of intraspinal neural stem cell grafts; directed differentiation improves outcome. Nat. Neurosci. *8*, 346–353.

Illes, J., Reimer, J.C., and Kwon, B.K. (2011). Stem Cell Clinical Trials for Spinal Cord Injury: Readiness, Reluctance, Redefinition. Stem Cell Rev. Published online April 8, 2011. 10.1007/s12015-011-9259-1.

Kakulas, B.A. (1999). The applied neuropathology of human spinal cord injury. Spinal Cord *37*, 79–88.

Keirstead, H.S., Nistor, G., Bernal, G., Totoiu, M., Cloutier, F., Sharp, K., and Steward, O. (2005). Human embryonic stem cell-derived oligodendrocyte progenitor cell transplants remyelinate and restore locomotion after spinal cord injury. J. Neurosci. *25*, 4694–4705.

Kennedy, P., and Rogers, B.A. (2000). Anxiety and depression after spinal cord injury: a longitudinal analysis. Arch. Phys. Med. Rehabil. *81*, 932–937.

Kimmelman, J. (2007). The therapeutic misconception at 25: treatment, research, and confusion. Hastings Cent. Rep. *37*, 36–42.

Kimmelman, J., and London, A.J. (2011). Predicting harms and benefits in translational trials: ethics, evidence, and uncertainty. PLoS Med. *8*, e1001010.

Kimmelman, J., Baylis, F., and Glass, K.C. (2006). Stem cell trials: lessons from gene transfer research. Hastings Cent. Rep. *36*, 23–26.

Knoepfler, P.S. (2009). Deconstructing stem cell tumorigenicity: a roadmap to safe regenerative medicine. Stem Cells *27*, 1050–1056.

Kovacsovics-Bankowski, M., Streeter, P.R., Mauch, K.A., Frey, M.R., Raber, A., van't Hof, W., Deans, R., and Maziarz, R.T. (2009). Clinical scale expanded adult pluripotent stem cells prevent graft-versus-host disease. Cell. Immunol. *255*, 55–60.

Kwon, B.K., Hillyer, J., and Tetzlaff, W. (2010). Translational research in spinal cord injury: a survey of opinion from the SCI community. J. Neurotrauma *27*, 21–33.

Lasiene, J., Shupe, L., Perlmutter, S., and Horner, P. (2008). No evidence for chronic demyelination in spared axons after spinal cord injury in a mouse. J. Neurosci. *28*, 3887–3896.

Lau, D., Ogbogu, U., Taylor, B., Stafinski, T., Menon, D., and Caulfield, T. (2008). Stem cell clinics online: the direct-to-consumer portrayal of stem cell medicine. Cell Stem Cell *3*, 591–594.

Levine, R.J. (1988). Ethics and Regulations of Clinical Research, Second Edition (New Haven, Connecticut: Yale University Press).

Lo, B., Zettler, P., Cedars, M.I., Gates, E., Kriegstein, A.R., Oberman, M., Reijo Pera, R., Wagner, R.M., Wuerth, M.T., Wolf, L.E., and Yamamoto, K.R. (2005). A new era in the ethics of human embryonic stem cell research. Stem Cells *23*, 1454–1459.

Maynard, F.M., Reynolds, G.G., Fountain, S., Wilmot, C., and Hamilton, R. (1979). Neurological prognosis after traumatic quadriplegia. Three-year experience of California Regional Spinal Cord Injury Care System. J. Neurosurg. *50*, 611–616.

Meletis, K., Barnabé-Heider, F., Carlén, M., Evergren, E., Tomilin, N., Shupliakov, O., and Frisén, J. (2008). Spinal cord injury reveals multilineage differentiation of ependymal cells. PLoS Biol. *6*, e182.

Miller, F.G., and Rosenstein, D.L. (2003). The therapeutic orientation to clinical trials. N. Engl. J. Med. *348*, 1383–1386.

Moon, L., and Bunge, M.B. (2005). From animal models to humans: strategies for promoting CNS axon regeneration and recovery of limb function after spinal cord injury. J. Neurol. Phys. Ther. *29*, 55–69.

Nature. (2004a). No consensus on stem cells. Nature *428*, 587.

Nature Neuroscience. (2004b). The promise of stem cells. Nat. Neurosci. *7*, 1013.

Nistor, G.I., Totoiu, M.O., Haque, N., Carpenter, M.K., and Keirstead, H.S. (2005). Human embryonic stem cells differentiate into oligodendrocytes in high purity and myelinate after spinal cord transplantation. Glia *49*, 385–396.

Norenberg, M.D., Smith, J., and Marcillo, A. (2004). The pathology of human spinal cord injury: defining the problems. J. Neurotrauma *21*, 429–440.

Popovich, P.G., Wei, P., and Stokes, B.T. (1997). Cellular inflammatory response after spinal cord injury in Sprague-Dawley and Lewis rats. J. Comp. Neurol. *377*, 443–464.

Popovich, P.G., Guan, Z., Wei, P., Huitinga, I., van Rooijen, N., and Stokes, B.T. (1999). Depletion of hematogenous macrophages promotes partial hindlimb recovery and neuroanatomical repair after experimental spinal cord injury. Exp. Neurol. *158*, 351–365.

Popovich, P.G., Guan, Z., McGaughy, V., Fisher, L., Hickey, W.F., and Basso, D.M. (2002). The neuropathological and behavioral consequences of intraspinal microglial/macrophage activation. J. Neuropathol. Exp. Neurol. *61*, 623–633.

Roy, N.S., Cleren, C., Singh, S.K., Yang, L., Beal, M.F., and Goldman, S.A. (2006). Functional engraftment of human ES cell-derived dopaminergic neurons enriched by coculture with telomerase-immortalized midbrain astrocytes. Nat. Med. *12*, 1259–1268.

Ruof, M.C. (2004). Vulnerability, vulnerable populations, and policy. Kennedy Inst. Ethics J. *14*, 411–425.

Schnell, L., Fearn, S., Klassen, H., Schwab, M.E., and Perry, V.H. (1999). Acute inflammatory responses to mechanical lesions in the CNS: differences between brain and spinal cord. Eur. J. Neurosci. *11*, 3648–3658.

Schwartz, M., and Yoles, E. (2006). Immune-based therapy for spinal cord repair: autologous macrophages and beyond. J. Neurotrauma *23*, 360–370.

Scott, C.T. (2008). Stem cells: new frontiers of ethics, law, and policy. Neurosurg. Focus *24*, E24.

Sellers, D.L., Maris, D.O., and Horner, P.J. (2009). Postinjury niches induce temporal shifts in progenitor fates to direct lesion repair after spinal cord injury. J. Neurosci. *29*, 6722–6733.

Sroga, J.M., Jones, T.B., Kigerl, K.A., McGaughy, V.M., and Popovich, P.G. (2003). Rats and mice exhibit distinct inflammatory reactions after spinal cord injury. J. Comp. Neurol. *462*, 223–240.

Steeves, J.D., Lammertse, D., Curt, A., Fawcett, J.W., Tuszynski, M.H., Ditunno, J.F., Ellaway, P.H., Fehlings, M.G., Guest, J.D., Kleitman, N., et al; International Campaign for Cures of Spinal Cord Injury Paralysis. (2007).

Guidelines for the conduct of clinical trials for spinal cord injury (SCI) as developed by the ICCP panel: clinical trial outcome measures. Spinal Cord *45*, 206–221.

Taoka, Y., Okajima, K., Uchiba, M., Murakami, K., Kushimoto, S., Johno, M., Naruo, M., Okabe, H., and Takatsuki, K. (1997). Role of neutrophils in spinal cord injury in the rat. Neuroscience *79*, 1177–1182.

Tetzlaff, W., Okon, E.B., Karimi-Abdolrezaee, S., Hill, C.E., Sparling, J.S., Plemel, J.R., Plunet, W.T., Tsai, E.C., Baptiste, D., Smithson, L.J., et al. (2010). A Systematic Review of Cellular Transplantation Therapies for Spinal Cord Injury. J. Neurotrauma. Published online April 20, 2010. 10.1089/neu.2009.1177.

Totoiu, M.O., Nistor, G.I., Lane, T.E., and Keirstead, H.S. (2004). Remyelination, axonal sparing, and locomotor recovery following transplantation of glial-committed progenitor cells into the MHV model of multiple sclerosis. Exp. Neurol. *187*, 254–265.

van der Bruggen, M.A., Huisman, H.B., Beckerman, H., Bertelsmann, F.W., Polman, C.H., and Lankhorst, G.J. (2001). Randomized trial of 4-aminopyridine in patients with chronic incomplete spinal cord injury. J. Neurol. *248*, 665–671.

Wade, N. (2005). Tracking the Uncertain Science of Growing Heart Cells. *New York Times*. Retrieved April 22, 2011 from http://www.nytimes.com/2005/03/14/health/14heart.html.

World Medical Association (WMA) (2008). WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects (http://www.wma.net/en/30publications/10policies/b3/index.html).

Yang, L., Blumbergs, P.C., Jones, N.R., Manavis, J., Sarvestani, G.T., and Ghabriel, M.N. (2004). Early expression and cellular localization of proinflammatory cytokines interleukin-1beta, interleukin-6, and tumor necrosis factor-alpha in human traumatic spinal cord injury. Spine *29*, 966–971.

Yang, H., Lu, P., McKay, H.M., Bernot, T., Keirstead, H., Steward, O., Gage, F.H., Edgerton, V.R., and Tuszynski, M.H. (2006). Endogenous neurogenesis replaces oligodendrocytes and astrocytes after primate spinal cord injury. J. Neurosci. *26*, 2157–2166.